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09/601,106	09/15/2000	Colin Anthony Kemp	T2328-906561	5597

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MILES & STOCKBRIDGE PC
1751 PINNACLE DRIVE
SUITE 500
MCLEAN, VA 22102-3833

EXAMINER	
CHOI, FRANK I	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/601,106
Filing Date: September 15, 2000
Appellant(s): KEMP, COLIN ANTHONY

Dennis P. Clarke
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 1, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

Claim 24 has not been rejected under 35 USC 112, second paragraph.

(7) Grouping of Claims

Appellant concedes that all of the appealed claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

STN/CAS online, file CAPLUS, Acc. No. 1987:446300, Doc. No. 107:46300, JP 61286327 (1986), Abstract.

Heaton et al. "Topical glyceryltrinitrate causes measurable penile arterial dilation in impotent men", The Journal of Urology (1990), Vol. 143, pp. 729-731.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 24-28 are rejected under 35 U.S.C. 102(b) as being anticipated by, or, in the alternative, as obvious under 35 U.S.C 103(a) over JP 61286327 (Abstract).

Claims 24-29 are rejected under 35 U.S.C. 103(a) as unpatentable over JP 61286327 (Abstract) in view of Heaton et al.

Claims 25-29 are rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention in that claim 25 does not indicate the claim number upon which it is dependent and claims 26-29 are dependent on claim 25.

The above rejections are set forth in a prior Office Action, mailed on January 28, 2004.

(11) Response to Argument

As a preliminary matter, although the JP 61286327 abstract is sufficient for purposes of the rejections herein, Examiner attaches, as Exhibit A, a copy of the Japanese Published Unexamined Patent Application (A) No. 61-286327, published December 16, 1986, and an English language translation thereof.

Claims 24-28 are rejected under 35 U.S.C. 102(b) as being anticipated by, or, in the alternative, as obvious under 35 U.S.C 103(a) over JP 61286327 (Abstract).

Although Appellant separately addresses anticipation and obviousness, the burden on Appellant in an inherency-based rejection under 35 USC 102(b)/103(a) is the same whether stated in terms of anticipation or obviousness. Appellant must show that the products of the Appellant and the prior art are not the same. See In re Spada, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990); In re Best, 195 USPQ 430, 433 (CCPA 1977) (where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established).

Appellant argues that it is impossible to ascertain the exact nature of the composition disclosed in the JP 61286327 abstract because said abstract recites "25%" to define the quantity of water in the water-containing lanolin and "1000 g" to define the amount of Vaseline®. The JP 61286327 abstract specifically recites an ointment "consisting of nitroglycerin 10, lactose 90, 25% H2O-contg. Lanolin 600, and white Vaseline to 1000 g." As such, "1000 g" is not the amount of Vaseline®. The term "1000 g" is the total weight of the ointment. As such, it is clear from the reference that 1000 grams of the ointment contains 10 grams of nitroglycerine, 90 grams of lactose and 600 grams of 25% water-containing lanolin (which calculates to 150 grams of water and 450 grams of lanolin), with the remaining portion being Vaseline®. This does not require a reading into the disclosure of the JP 61286327 abstract any limitations that are not present or cannot reasonably be discernible from the abstract itself. As such, the mere fact that the JP 61286327 abstract uses "25%" and "1000 g" is insufficient to support a conclusion that

the exact components of the prior art composition are impossible to ascertain or that the reference is fatally confusing and vague.

Therefore, in light of the above, the 35 USC 102(b)/103(a) rejection of claims 24-28 over JP 61286327 (Abstract) is proper.

Claims 24-29 are rejected under 35 U.S.C. 103(a) as unpatentable over JP 61286327 (Abstract) in view of Heaton et al.

Contrary to Appellant's arguments, the JP 6129637 abstract is not deficient for the same reasons as above, as such, a skilled artisan would be able to readily ascertain the operable amounts. Further, Examiner has not acknowledged that the prior art does not disclose the amounts of ingredients specified in the claims. Examiner has only acknowledged that the prior art does not expressly disclose a composition or product "consisting essentially of 10 wt% glyceryl trinitrate (10% in lactose), 44 wt% lanolin, 21 wt% white soft paraffin B.P. and 25 wt% demineralized water" (See Office Action (1/28/2004), Pg. 4), i.e. the limitations set forth in claim 29 which is dependent on claims 24 or 25. However, since Appellant concedes that the claims stand and fall together, if the rejection of claim 24 or claim 25 is valid than claim 29 falls with said claims. See In re Weijlard, 69 USPQ 86 (CCPA 1946). Claim 24 recites a composition for treating erectile dysfunction comprising a mixture of effective amounts of glyceryl trinitrate and lanolin and also containing water, whereas, claim 25 recites a cosmetic product comprising the composition of an unidentified claim which apparently includes a mixture of effective amounts of glyceryl trinitrate and lanolin and also containing water.

As indicated above, the JP 61286327 abstract discloses an ointment which contains, in 1000 grams of said ointment, 10 grams of nitroglycerine and 600 grams of 25% water-containing

lanolin which calculates to 1% by weight nitroglycerine, 45% by weight lanolin and 15% by weight water based on the total weight of the ointment. Other than arguing that the amounts disclosed in the JP 61286327 abstract cannot be ascertained and unsupported conclusions relative to hind site reconstruction, Appellant does not appear to have presented any other arguments or evidence that the ointment disclosed in the JP 61286327 abstract does not meet the limitations of the claimed invention as represented by claim 24 or claim 25. See In re Lemin, 140 USPQ 273,276 (CCPA 1964) (subject matter as a whole must be considered under 35 USC 103, but, in applying the statutory test, the differences over the prior art must be more substantial than a statement of intended use of old composition; no indication that claimed amount which was defined by functional language was any different from a therapeutic amount that one skilled in the art of the prior art would select). Combining the teachings of the JP 61286327 abstract with Heaton et al. does not invalidate the rejection.

Appellant presents no basis for concluding that Appellant's disclosure was used as a template, that the teachings of the JP 61286327 abstract and Heaton et al. are isolated disclosures from two separate references containing disparate and unrelated teachings, or that the references do not suggest that the references can be combined. "Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from Appellant's disclosure, such a reconstruction is proper." In re McLaughlin 170 USPQ 209, 212 (CCPA 1971).

Appellant's reliance on Ex parte Walker, 135 USPQ 195 and Ex parte Fleischmann, 157 USPQ 155, to argue that it must be physically possible to combine the references, is misplaced.

Said cases do not reflect the current state of the law. "The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." In re Keller, 208 USPQ 871, 881 (CCPA 1981). See also In re Sneed, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review.").

Further, the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Kotzab, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); In re Eli Lilly & Co., 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); In re Nilssen, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); and Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). Also, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by Appellant. See In re Linter, 173 USPQ 560 (CCPA 1972); In re Dillon, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991).

The JP 61286327 abstract discloses a topical pharmaceutical containing a small amount of nitroglycerin for accelerating peripheral blood circulation and skin respiration in the form of an ointment that includes nitroglycerine, lanolin and water (JP 61286327, Abstract). Heaton et al. discloses that topically applied nitroglycerine is effective in dilating arterial blood vessels and treating erectile dysfunction. (Heaton et al., Materials and Methods, Results, Pgs. 729, 730). As such, in view of the teachings of Heaton et al., one of ordinary skill in the art would expect that the ointment disclosed in the JP 61286327 abstract would also be suitable for treating erectile dysfunction since it contains nitroglycerine, is applied topically and accelerates peripheral blood circulation.

Appellant's argument that Heaton et al. teaches away from the claimed invention is insufficient to rebut the *prima facie* case of obviousness. Heaton et al. does not disclose that 40% of the subjects tested complained of headache. Heaton discloses that out of a total 174 patients tested there were no significant side effects but 56 men complained of headache with the results of 140 of the 174 patients being evaluated (Heaton et al., Pg. 729, Materials and Methods, Results). Appellant does not appear to show how a non-significant side effect of headache contraindicates the safety and efficacy of the reference composition, much less, teaches away from the claimed invention. In any case, the safety of a product does not determine the issue of obviousness. See Nickola v. Peterson, 193 USPQ 443,447 (DC EMich 1976) ("Whether persons of ordinary skill in the art disagree as to the safety of a product or techniques does not determine the issue of obviousness. The issue regarding obviousness is whether the differences embodied in a combination product and the result so produced would have been non-obvious to a person of ordinary skill in the art, not whether there was a controversy over whether such was safe"); see

also, In Re Jansen, 187 USPQ 743,745,746 (CCPA 1975). Further, the non-significant side effect of headache does not alter the fact that, as indicated above, Appellant has not shown that the ointment disclosed in the JP 61286327 abstract does not contain a mixture of effective amounts of nitroglycerin and lanolin. As such, the non-significant side effect of headache does not appear to contraindicate the efficacy of the reference composition.

Therefore, in light of the above, the 35 USC 103(a) rejection of claims 24-29 over JP 61286327 (Abstract) in view of Heaton et al. is proper.

Claims 25-29 are rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention.

Appellant argues that the rejection of claims 25-29 under 35 USC 112, 2nd paragraph, should be reversed since claim 25 recites all of the ingredients present in the inventive composition. Although claim 25 recites glyceryl trinitrate, lanolin and water, claim 25 does not specifically recite the use of a solid stabilizer, lactose and/or white soft paraffin B.P.. Since a solid stabilizer, lactose and/or white soft paraffin B.P. are set forth in one or more of the claims dependent on claim 25, the same are clearly part of at least one embodiment of Appellant's alleged "inventive composition". However, since claim 25 does not require the presence of a solid stabilizer, lactose and/or white soft paraffin B.P., claim 25 does not necessarily recite all of the ingredients present in the alleged "inventive composition". In any case, whether or not claim 25 recites all of the ingredients present in the alleged "inventive composition", said argument fails to address the issue. The issue is that the language of claim 25 by its terms requires one to look to an unidentified claim to determine the components of the composition, and, thus, one of

ordinary skill in the art would not be apprised of the metes and bounds of claim 25 or claims 26-29 which are dependent directly or indirectly on claim 25.

Therefore, in light of the above, the rejection of claims 25-29 under 35 USC 112, 2nd paragraph is proper.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Frank Choi
December 27, 2004

Conferees
Gary Kunz, SPE
John Pak, Primary Examiner

JOHN PAK
PRIMARY EXAMINER
GROUP 1600

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

MILES & STOCKBRIDGE PC
1751 PINNACLE DRIVE
SUITE 500
MCLEAN, VA 22102-3833

EXHIBIT A

Japanese Published Unexamined Patent Application (A) No. 61-286327, published December 16, 1986, and English language translation thereof.

⑲日本国特許庁（JP）　⑪特許出願公開

⑫公開特許公報（A）　昭61－286327

⑤1Int.Cl.⁴		識別記号	庁内整理番号	⑬公開　昭和61年(1986)12月16日
A 61 K	31/21	ABN	7330－4C	
	9/06	AAS		
	9/10			
	9/18			
	31/21	ABR		
		ADA		
// C 07 C	77/04			審査請求　未請求　発明の数 1　(全3頁)

⑤4発明の名称　局所外用剤

⑳特　願　昭60－126425
㉒出　願　昭60(1985)6月12日

⑦2発明者　黒野　昌庸　名古屋市南区駈上1－7－17
⑦2発明者　山崎　泰右　愛知県海部郡甚目寺町甚目寺郷浦10－1
⑦2発明者　犬飼　勉　名古屋市東区東外堀町35番地　株式会社三和化学研究所内
⑦1出願人　株式会社　三和化学研究所　名古屋市東区東外堀町35番地
⑦4代理人　弁理士　佐々木　功

明　細　書

1．発明の名称

局所外用剤

2．特許請求の範囲

(1) 末梢血管における循環促進用及び皮膚呼吸促進用の局所外用剤において、少量のニトログリセリンを主成分としていることを特徴とする、局所外用剤。

(2) レーノー症候群の治療に用いることを特徴とする、特許請求の範囲第1項に記載の局所外用剤。

(3) 凍傷の治療に用いることを特徴とする、特許請求の範囲第1項に記載の局所外用剤。

(4) 強皮症の治療に用いることを特徴とする、特許請求の範囲第1項に記載の局所外用剤。

(5) 皮膚移植に際し移植用皮膚の前処理に用いることを特徴とする、特許請求の範囲第1項に記載の局所外用剤。

(6) 皮膚移植部の前処理及び移植後の治療に用いることを特徴とする、特許請求の範囲第1項に記載の局所外用剤。

3．発明の詳細な説明

（産業上の利用分野）

本発明は局所外用剤に係り、殊に末梢血管における循環促進用及び皮膚呼吸促進用に用いられる局所外用剤に係る。

（従来の技術）

従来、局所末梢血管における循環障害例えばレーノー症候群、凍傷、強皮症等の治療に際しての局所外用剤としてはビタミン類例えばビタミンEや、ホルモン例えば副腎皮質ホルモンが配合され、場合によりカンフルが更に配合された軟膏剤が主として使用されて来た。

（発明の背景）

ニトログリセリンは冠血管拡張作用を有し、狭心症の発作時においてその抑制のために、及び発作予防を目的として汎用されている。これら目的で使用されるニトログリセリン製剤は全身作用を対象としており、現在我国では経口剤又は坐剤の形で使用されているが、本出願人会社は経皮吸収

により全身作用をもたらすニトログリセリン外用剤の研究を従来から行なって来ており（例えば特願昭５３－７３７９２及び同５３－１４５２７３号）、現在も実用化に向けての研究を継続中である。

本発明者等はニトログリセリンの薬理作用につき更に更に研究を重ねた結果、少量を経皮吸収させる場合にニトログリセリンは局所血管拡張作用を示し、局所末梢血管における循環促進をもたらすこと並びに皮膚吸収の促進をもたらすことを見出したのである。

（発明の目的）

従って、本発明の主たる目的は、局所末梢血管における循環障害に基因する各種疾患、殊にレーノー症候群、凍傷、強皮症等の治療に適するニトログリセリン外用剤を提供するとにある。

本発明の付随的目的は、皮膚移植における移植用皮膚の前処理や移植部の前処理及び移植後の局所治療剤として好適なニトログリセリン外用剤を提供することである。

（目的を達成するための手段及び作用）

本発明によれば、上記目的は、少量のニトログリセリンを主成分とする局所外用剤により達成される。

本発明による局所外用剤には気散防止剤、安定化剤、吸収促進剤等が配合されていることができる。製剤化は常法により行われ、剤型はクリーム剤、ゲル軟膏剤、液剤、貼付剤等の任意の外用形態であることができる。

本発明による局所外用剤に配合されるニトログリセリンの量は疾患の種類、症状等に依存して決定されるべきものであるが、使用量としては１日当り６■ｇ以下が好ましい。

（発明の効果）

本発明による局所外用剤はその主成分として配合されるニトログリセリンが少量であり、皮膚呼吸の促進及び局所末梢血管における循環促進により疾患の治癒をもたらそうとするものであるから、従来のホルモン系皮膚再生剤等と比較して使用安全性に優れている。

（製剤例等）

次に、本発明による局所外用剤の製剤例及び薬効薬理試験例について説明する。

製剤例１　（軟膏剤）

下記諸成分を配合し、常法により軟膏剤を製造した。この軟膏剤は１ｇ中にニトログリセリンを１０■ｇ含有している。

ニトログリセリン乳糖１０倍散	１００（ｇ）
２５％加水ラノリン	６００
白色ワセリン	残　部
計	１０００（ｇ）

製剤例２　（外用液剤）

下記諸成分を配合し、常法により外用液剤を製造した。この外用液剤は１■ℓ中にニトログリセリンを１０■ｇ含有している。

ニトログリセリン　サイクロデキストリン包接１０倍散	１００（ｇ）
ジフェニルヒドラミン	２０（■ℓ）
グリセリン	２５０（ｇ）
トラガント	５０（ｇ）

精製水	残　部
計	１０００（■ℓ）

製剤例３　（クリーム剤）

下記諸成分を配合し、常法によりクリーム剤を製造した。このクリーム剤は１ｇ中にニトログリセリンを５■ｇ含有している。

ニトログリセリン　サイクロデキストリン包接１０倍散	５０（ｇ）
安息香酸ナトリウム	５
セバチン酸ジエチル	１００
鯨蝋	４０
ポリオキシエチレンオイルエーテル	
燐酸ナトリウム	６０
ワセリン	残　部
計	１０００（ｇ）

薬効薬理試験例　１

（凍傷治療）

体重３００±１０ｇのwister系雄性ラット１群３匹を用い、ドライアイスで尾部に凍傷を誘発させた。次いで試験区では製剤例１による軟膏剤５

0mg（ニトログリセリンとして0．5mg含有）を凍傷部に塗布して治癒を施こした。

数日後に試験群と無処置の対照群における凍傷部位を調べた処、対照群には壊疽性凍傷が認められ、一方試験群にも紅斑性凍傷が認められるも対照群における凍傷の程度とは明白な相違が観察され、ニトログリセリンが凍傷に関する初期治療効果を有していることが判明した。

薬効薬理試験例　2

（末梢血管拡張作用）

家兎の耳部を根元から切断し、耳介後動脈にリンゲル液注入用装置を接続してKrawkow－Plsseaski法により耳介前静脈からのリンゲル液の滴出量を受滴器にて測定した。

本発明による局所外用剤50mg（製剤例1による軟膏剤であって、ニトログリセリンとして0．5mg含有）を塗布した処、塗布後数分で滴出量に30％以上の増加が認められ、ニトログリセリンが末梢血管拡張作用を有していることが明確となった。

薬効薬理試験例　3

（皮膚移植試験）

体重300±10gの雄性モルモット1群3例を用い、エーテル麻酔下で背部除毛後に電気ゴテにより1～2cm²範囲の局所熱傷を受傷させ、熱傷面にはペニシリンプロカイン液を塗布し、通気性テープで固定カバーした。

受傷7日後に、エーテル麻酔下で腹部にニトログリセリン軟膏50mg（製剤例1によるものであって、ニトログリセリンとして0．5mg含有）を塗布し、30分後にこの軟膏残留物を拭取り、洗浄し、次いで採皮刃にて皮膚を1～2cm²程度採取し、これを専用ヘラに展張させると共に、採皮部については常法により閉鎖処置した。

一方、前記熱傷による壊死層については同様に採皮刃にて出血が認められる健常組織部に達する層部分に至る迄切除し、壊死層の除去後にアドレナリン溶液を浸したガーゼにて止血処置し、専用ヘラで展張させた上記皮膚片を移植した。移植皮膚の表面をガーゼで圧迫固定し、次いで上部に通

気性テープを貼付して固定させた。植皮処置後12時間毎にバルビタールを2回筋注して安静状態に保った。植皮から5日後に植皮部を開被し、1日1回10日間に亘り製剤例3のクリーム剤を塗布して施療し（1回当りの使用量は1g以下であり、ニトログリセリンの含量として5mg以下であった）、植皮状況を観察した。

結果は下記表に示される通りであり、未処置の対照群及び移植用皮膚に前処理を施した試験群には共に3例中1例の死亡例があったが、移植用皮膚に前処理を施こし且つ移植後にも施療した試験群には死亡例はなく、更に対照群においては植皮が不完全であったが、両試験群では全例植皮に成功した。

	観察結果
対照群（未処置）	不良（2例）
試験群	
移植前処理のみ	良　（2例）
移植前処理と植皮後の施療併用	優良（3例）

薬効薬理効果試験例　4

寒冷時に手指にヒビレ感があり末梢血管障害の可能性があるボランティア3名に、製剤例3のクリーム剤を提供し、これを1ケ月に亘りハンドクリームとして適時使用させ、その後にアンケート調査した処、次の結果が得られた。

使用感：

稍々ベトツキ使用しにくい……2名

良好と思う……1名

症状の改善：

改善効果あり……3名

改善効果なし……0名

上記結果から、使用感を良化するために基剤組成に改良の余地があるも、血行を改善して手指のヒビレ感を緩和乃至解消させるのに有効であることが判明した。

特許出願人　株式会社　三和化学研究所

代理人　弁理士　佐々木　功

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Locally Applicable External Medicine

CLAIM(S)

1) A locally applicable external medicine containing a small amount of nitroglycerin as a primary component and being effective for accelerating the circulation of peripheral blood vessels and for accelerating the skin breathing.

2) A locally applicable external medicine, as cited in Claim 1, characterized in that it can be used for treating a Raynaud's syndrome.

3) A locally applicable external medicine, as cited in Claim 1, characterized in that it can be used for treating congelation.

4) A locally applicable external medicine, as cited in Claim 1, characterized in that it can be used for treating scleroderma.

5) A locally applicable external medicine, as cited in Claim 1, characterized in that it can be used for pretreating the skin to be transplanted at a time of transplanting a skin.

6) A locally applicable external medicine, as cited in Claim 1, characterized in that it can be used for pretreating the skin-transplanting section and post-treating the transplanted skin section.

DETAILED DESCRIPTION OF THE INVENTION

(Field of Industrial Application)

The present invention pertains to an external medicine to be applied to local areas, particularly the medicine used for accelerating the blood circulation in peripheral blood vessels and for aiding cutaneous breathing.

(Prior Art)

In the past, as an external medicine to be applied to local areas for treating circulation problems in local peripheral blood vessels, e.g., in Raynaud's syndrome, congelation, and scleroderma, an ointment mixed with vitamins, e.g., vitamin E, or adrenal cortex hormone, and camphor, if needed, was primarily used.

(Background of Invention)

Nitroglycerin has a vessel expansion function, and is generally used at a time of cardiac arrest and for its prevention. The nitroglycerin medicine aims at acting on an entire body. At present, it is used in form of oral intake tablet or suppository. The applicant of the present invention has continued the research on a nitroglycerin external medicine that is endermic and acts on the entire body (For example, Japanese Patent Applications 53-073792 and 53-145273), and its medical application is now being researched.

As a result of continuous research on the pharmaceutical function of nitroglycerin, the applicant found that nitroglycerin demonstrated a local blood vessel expansion function when applied to skin by a small amount and that it invigorates the blood circulation in local peripheral vessels.

(Objective)

The present invention attempts to present a nitroglycerin agent for external use that is applicable to treatment of various diseases caused by circulation obstruction in local peripheral blood vessels, e.g., Raynaud's syndrome, congelation, and scleroderma.

An additional objective of the present invention is to present a nitroglycerin external agent applicable to pretreatment and posttreatment of skin transplant and to local treatment of the transplanted section.

(Means to Accomplish the Objective and Function)

According to the present invention, said objective is accomplished by a locally applicable external medicine primarily containing a small amount of nitroglycerin.

In the locally applicable external medicine of the present invention, a dissipation-preventing agent, a stabilizer, and an absorption accelerator can be mixed. Manufacture of the agent can be performed by a conventional method, and it can take a properly selected external medicine form, cream, ointment in gel form, liquid form, or patch form.

The amount of nitroglycerin mixed in this locally applicable external agent is determined by types of disease and symptom, but a preferred amount to be used is 6 mg a day.

(Effect of Invention)

With the locally applicable external medicine of the present invention, a small amount of nitroglycerin is used as a primary component, and it is meant to treat diseases by aiding cutaneous breathing and accelerating the blood circulation in local blood vessels, therefore, is safer than the prior art skin reproduction agent using a hormone agent.

(Examples of Manufacture)

Manufacture of this locally applicable external medicine and its medical effect are explained below.

Example 1 (Ointment)

The following components were mixed and the ointment was made by the conventional method. This ointment contained nitroglycerin 10 mg in 1 g of ointment.

Nitroglycerine lactose 10 times dispersion	100 g
25% water-added lanolin	600
white vaseline	remaining portion
Total	1,000 g

Example 2 (Liquid agent for external application)

The following components were mixed and a liquid agent for external application was made. In this liquid agent 1ml for external application, nitroglycerin was contained by 10 mg.

Nitroglycerin cyclodexitrin inclusion 10 times	100 g
Diphenyl hydramine	20 ml
Glycerin	250 g
Tragacanth	50 g
Purified water	remaining portion
Total	1,000 ml

Example 3 (Cream)

The following components were mixed and the agent in cream form was made. This cream 1 g contained nitroglycerin 5 mg.

Nitroglycerin cyclodextrin inclusion 10 times dispersion 50 g

Sodium benzoate	5
Diethyl sebacate	100
Whale wax	40 g
Polyoxy ethylene oil ether sodium phosphate	60 g
Vaseline	remaining portion
Total	1,000 g

Medical effect test example 1 (Treatment of congelation)

A group of 3 wister male rats having weight 300 +/- 10 g was used. Their tails were put to freeze to cause congelation. The ointment (containing 0.5 mg of nitroglycerin) of manufacture example 1 was applied by 50 mg to the congelation sections of rats in the test group.

In a few days, the test group and untreated reference group were compared. It was found that the reference group had a serious congelation but the test group had much less serious congelation. Accordingly, it was evident that the nitroglycein has an effect for treating congelation in incipient stage.

Medical effect test example 2 (Peripheral vessel expanding effect)

An earlobe of a mouse was cut off from the root. A Ringer,s solution injection device was connected to the artery behind the ear, and by the

Krawkow – Pissemski method, the amount of Ringer's solution extracted from the artery before the ear was measured.

When the locally applicable ointment of the present invention 50 mg (ointment of manufacture example 1 that contains 0.5 mg of nitroglycerin) was applied. The extracted amount was increased 30% or more in a few minutes after application. Thus, it was confirmed that nitroglycerin had a peripheral vessel expanding function.

Medical effect test example 3 (Test for skin transplant)

Male guinea pigs in 3 groups with weight 300 +/- 10 g were used. Their back hairs were removed after doping them with ether and the back sections were locally burned by 1 – 2 cm^2 range with an electrical iron. A penicillin procaine solution was applied to the burned surface, which then was covered with an air-permeable tape.

In 7 days after this injury, nitroglycerin ointment 50 mg (the manufacture example 1 that contains nitroglycerin 0.5 mg) was applied to a stomach section after doping with ether. This ointment residue was cleaned away in 30 minutes, and about 1 – 2 cm^2 of stomach skin was removed and expanded on a special spatula while at the same time the stomach section was treated by the conventional method.

On the other hand, the dead skin layer made by said burn injury was cut away with a skin cutting knife down to the layer having a normal healthy tissue where bleeding was observed. The bleeding-stopping treatment was applied immediately following the removal of dead skin layer with a gauze soaked with adrenaline, and said skin expanded on the special spatula was transplanted. The surface of the transplanted skin was pressed with a gauze and an air-permeable tape was patched on it. After the skin transplant, a barbital was injected into the tissue every 12 hours twice to sedate it. In 5 days after the skin transplant, the transplanted skin section was uncovered. Then, the cream of manufacture example 3 was applied once a day for 10 days (The dosage per 1 application was less then 1 g which contained nitroglycerin 5 mg or less.) for treatment, and the transplanted skin condition was examined.

The result is shown in the table below. With the untreated reference group and the group for which the pretreatment was done to the skin for transplanting, 1 out of 3 guinea pigs died, but in the test group for which pretreatment was done to the skin for transplanting and treatment was done after transplanting, there was no death. In the reference group, the skin transplant was not perfect, but the skin transplant was successful and perfect with every example of guinea pig in both test groups.

	Result of observation
Reference group (untreated)	Not good (2 examples)
Tested group	
Treated only before transplant	Good (2 examples)
Treated before and after transplant	Excellent (3 examples)

Medical effect test example 4

The cream of manufacture example 3 was provided to 3 volunteers who were experiencing numbness on fingers in cold weather. They used this cream at proper times for 1 month as a hand cream, and their responses were examined. The result is as follows.

Feel when used:

Sticky……..2 people

Pretty good…… 1 person

Improvement to symptom:

There was an improvement……3 people

No improvement……..0

From the above result, it became evident that the cream was effective in improving the blood circulation and in eliminating or reducing the numbness on the fingers.

Translations
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Akiko Smith